Chapter 5

Concerns with β2-agonists in Pediatric Asthma - a Clinical Perspective -

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Submitted

ABSTRACT

Beta2-adrenoreceptor agonists (β2-agonists) are extensively used in the treatment of childhood asthma. However, there have been concerns regarding their adverse effects and safety. In 2005, the FDA commissioned a "Black Box Warning" communicating the potential for an increased risk for serious asthma exacerbations or asthma-related death with the regular use of LABAs. In a meta-analysis of controlled clinical trials the incidence of severe adverse events appeared to be highest in the 4-11 year age group. Several mechanisms have been proposed to explain this, such as masking patients' perception of worsening asthma, desensitization and downregulation of the β2-adrenoreceptor, pro-inflammatory and pro-asthmatic effects of β2-agonists, pharmacogenetic effects of β2-adrenoreceptor polymorphisms and age related differences in pathophysiology of asthma.

In this paper, we review β2-receptor pharmacology, discuss the concerns regarding treatment with β2-agonists in childhood asthma and exercise induced bronchoconstriction, and provide suggestions for clinical pediatric practice in the light of current literature.

Contents

INTRODUCTION & HISTORICAL BACKGROUND

Beta2-adrenoreceptor agonists (β2-agonists) are extensively used in the treatment of childhood asthma. Short acting β2-agonists (SABAs) are the first choice as rescue medication during acute bronchoconstriction and provide protection against exercise induced bronchoconstriction (EIB).[1] SABAs activate the β2-adrenoreceptor (β2AR) within 5 min and have a bronchodilator effect of 4-6h.[2] Long acting β2-agonists (LABAs) have a longer (12-24h) bronchodilator effect.[2] Currently, in clinical guidelines for children, LABAs are recommended as one of the step-up options for maintenance treatment in combination with inhaled corticosteroids (ICSs) when asthma is not adequately controlled with ICSs alone.[3,4]

Adrenergic receptor agonists are one of the oldest classes of drugs used in medicine. Sympathomimetic agents were already used in Chinese herbal medicine to relieve breathing problems as early as 3000 BC.[5] Adrenaline was the first "modern" sympathomimetic drug that was used to relieve asthma symptoms. As concerns about possible cardiotoxicity and the development of tolerance rose, drugs with a greater selectivity for airway smooth muscle were developed. The first non-selective β-receptor agonist, isoproterenol (isoprenaline), was developed in the 1940s. Isoproterenol was still associated with severe side effects such as tachycardia and palpitations through its effects on the β1-receptor. The discovery that there were more types of adrenergic receptors led to the classification of α- and β-receptors, and subclassification of β1- and β2-receptors. This resulted in the development of more selective β2-agonists in the 1960s.

In 1956 the first pressurized metered-dose inhaler was invented[6] and aerosol technology developed rapidly in the subsequent decades. The bronchoprotective effect of inhaled β-agonists against EIB in children was demonstrated.[7] Inhalation of β2-agonists was shown to provide a better effect and fewer cardiovascular side effects than oral or intravenous administration.[8,9]

The short duration of action of SABAs was a problem for patients who needed protection for a longer period, particularly at night. This led to the development of salmeterol, which was marketed in 1990, and the discovery of formoterol soon after. Both drugs have a prolonged effect leading to bronchodilation for ≥ 12h. Novel ultra-long-acting β2-agonists with a duration of action of approximately 24h have recently been registered for adults and children > 12 years.[10]

In the past 20 years, concerns about the safety of LABAs caused an ongoing controversy among drug authorities, scientists and clinicians[11,12], as meta-analyses indicate a significantly higher risk of serious adverse events, such as life-threatening asthma exacerbations[13-20], in adults and children regularly taking LABAs. Particular concern has risen about the risk of LABAs in childhood asthma.[19,21] Approval for LABA/ICS combination therapy by the US Food and Drug Administration (FDA) for children aged 4-11 years was primarily based on extrapolation of efficacy studies performed in adolescents and

adults.[3] However, in contrast to data in adults, pediatric studies do not show a significant superior effect of adding a LABA compared to increasing the dose of ICS on asthma control and quality of life, but do show improved lung function and growth.[22,23]

In this paper, we discuss the concerns regarding treatment with β2-agonists in childhood asthma and EIB, review β2-receptor pharmacology, and focus on clinical recommendations for pediatricians in the light of current literature.

PHARMACOLOGY

The adrenoreceptors are a class of G-protein coupled receptors that are targeted by catecholamines. There are two main groups of adrenoreceptors, α- and β-receptors, with several subtypes including β1- and β2-receptors. The β2AR predominates in the respiratory tract, where it is widely distributed, not only in airway smooth muscle cells (with a density of 30.000-40.000 receptors per cell), but also in lung epithelial cells, endothelial cells and inflammatory cells that reside in the airways.[24] The receptor density increases more distal throughout the respiratory tract with highest levels in the central lung and alveolar region.[24]

Stimulation of the β2AR in airway smooth muscle cells induces a signal transduction pathway, resulting in increased intracellular cyclic-3',5'-adenosine monophosphate (cAMP).[2] cAMP catalyzes the activation of protein kinase A (PKA), which subsequently leads to phosphorylation of key regulatory proteins involved in the control of muscle tone. An increase in cAMP inhibits Ca^{2+} release from intracellular stores, reduces Ca^{2+} entry into the cells, and enhances sequestration of intracellular Ca^{2+}. The G-protein also directly interacts with potassium channels present in the airway smooth muscle cell membrane, without involving cAMP. Both cAMP-dependent and -independent processes finally result in airway smooth muscle relaxation (Fig. 1).

Stimulation of the β2AR in the mast cells leads to mast cell stabilization through an increase in intracellular cAMP.[25] β2-Agonists inhibit the release of pre-stored histamine from mast-cells, and the synthesis of new mediators, such as cysteinyl leukotrienes and prostaglandin D2.

Stimulation of the β2AR on epithelial cells leads to an increased beat frequency of cilia and may therefore facilitate mucociliary clearance.[26] Furthermore, β2-agonists inhibit extravasation of plasma proteins in the airway wall, thereby reducing the airway wall congestion that contributes to airway obstruction in asthma.[26]

Prolonged exposure to an agonist desensitizes G-protein-coupled receptors. In homologous desensitization, within minutes of binding of a ligand to its receptor, G-protein receptor kinase is activated. This kinase phosphorylates the carboxyterminal lis of the G-protein-coupled receptor, which changes the receptor conformation and leads to

decoupling of the receptor from the G-protein, resulting in receptor subsensitivity. In heterologous desensitization the receptor is phosphorylated by a non-specific kinase that was activated by binding of a ligand to a different G-protein coupled receptor.

β-Arrestin binds to the phosphorylated receptors, after which they are internalized by endocytosis. The internalized receptors can be recycled to the cell membrane. However, when exposure to the ligand or agonist continues, the total transit time for the recycling of receptors increases[24] and part of the receptors will be degraded in lysosomes. After hours of agonist exposure, there is a net loss of receptors, called downregulation.[24] The receptors can only be replaced by re-synthesis of new receptors through transcription of the β2AR-gene.[24,26] However, activation of the β2AR inhibits this transcription. Therefore it takes hours to days to overcome downregulation.

Corticosteroids increase β2AR-gene transcription and regulate both the number of receptors and the coupling to adenylate cyclase. Systemic corticosteroids can reverse β2AR downregulation.[24]

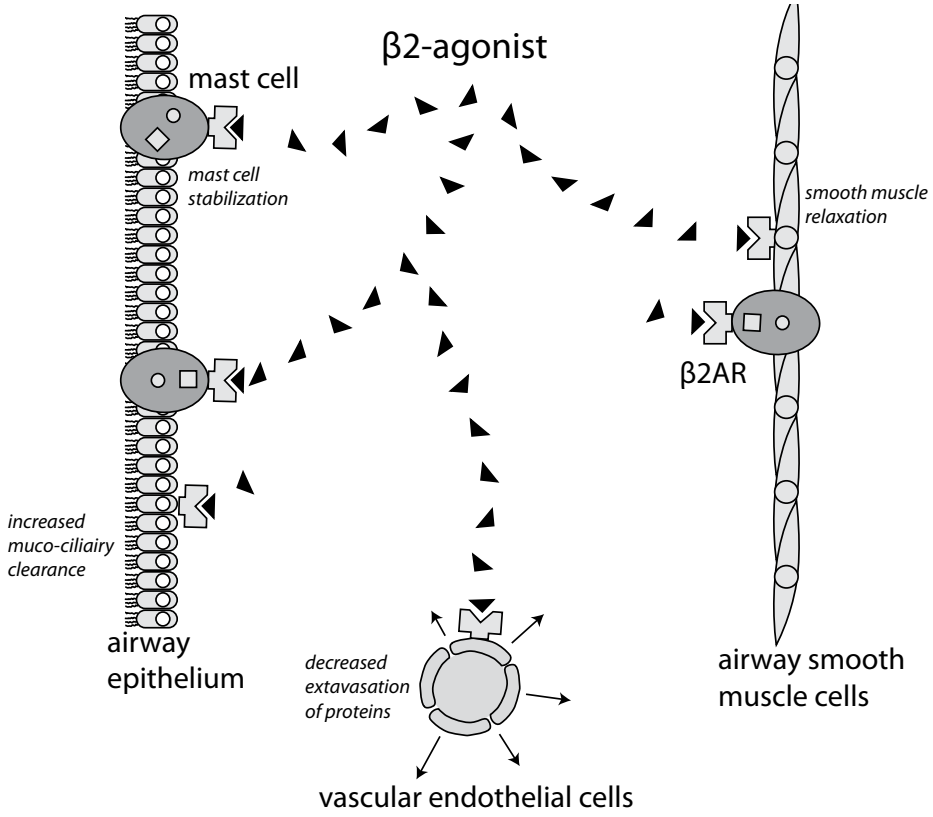

Fig. 1. Physiological effects of β2-agonists in the airways.
β2AR = β2-adrenoreceptor.

CONCERNS WITH REGULAR β2-AGONIST TREATMENT

No large efficacy and safety studies were performed when SABAs were introduced. Two epidemics of asthma related mortality, after the marketing of isoproterenol in the 1960s in the United Kingdom[27] and fenoterol in the 1970s in New Zealand[28], rose concern about regular SABA treatment. It was assumed that the relationship between asthma mortality and isoproterenol (a non-selective β-agonist) resulted from cardiac toxicity, and it was postulated that the dose related effect of fenoterol on asthma mortality[29] reflected increased SABA use due to more severe asthma. However, a prospective trial by Sears et al. in adolescent and adult asthmatics (aged 15-64y) in 1990 demonstrated worse asthma control when fenoterol was used regularly compared to when it was used as rescue, as-needed therapy.[30] Several placebo controlled studies have since then compared the effect of regular treatment with a SABA to as-needed treatment in adults.[31] Overall, there was little evidence to support regular use of SABAs[31] and SABAs are therefore advised to use only on an 'as needed' basis. Increased use is considered to indicate a deterioration of asthma control and the need to step-up treatment.

As SABAs are recommended to be used on an as needed basis, it seems inconsistent to recommend regular use of LABAs. Since the introduction of LABAs there have been concerns regarding their adverse effects and safety, leading to large scale studies. Among the first studies were the Serevent Nationwide Surveillance Study (SNS)[32] and Salmeterol Multi-center Asthma Research Trial (SMART).[33] The SNS study was a 16-week, double-blind study in 25,180 subjects aged ≥ 12y that found a statistically insignificant increase in the number of asthma-related deaths in patients treated with salmeterol twice daily compared to four times daily salbutamol (RR 3.0, 95% CI 0.7–20). The SMART trial was a 28-week, randomized, placebo-controlled trial in 26,355 subjects aged ≥ 12y that found a significantly increased risk for asthma-related death (RR 4.37, 95% CI 1.25–15.3) and respiratory related death (RR 2.16, 95% CI 1.06-4.41) in patients treated with salmeterol. On subgroup analysis, this increased risk was only found in African-Americans.

SMART was not adequately designed to determine whether or not ICS use affected the incidence of asthma or respiratory related deaths, but the vast majority of deaths occurred in patients who did not receive ICS.

These observations led to a "Black Box Warning" by the FDA in 2005 communicating the potential for an increased risk for serious asthma exacerbations or asthma-related death with the regular use of LABAs. Subsequently, over a dozen meta-analyses investigating the adverse effects of LABAs in adults and children were published, providing an equivocal picture.[13-20,34-40] Some of these meta analyses demonstrated an increased risk of serious adverse events, such as hospitalizations, life-threatening exacerbations and asthma-related death with LABA use compared to placebo,[13-20] while others did

not.[34-40] This inconsistency is probably due to differences in background therapy and heterogeneity in study design and study populations.

In some meta-analyses, subgroup analyses suggested that combination therapy with an ICS protects against asthma-related serious adverse events.[19,20,40,41] Two recent Cochrane meta-analyses assessed the safety of LABA/ICS combination therapy versus ICS monotherapy.[36,37] In adults and children on salmeterol with ICS compared to ICS monotherapy, there was no significant difference in overall deaths, asthma-related deaths or non-fatal serious adverse events.[37] However, a trend towards an increase in asthma related deaths in adults (OR 3.6, 95% CI 0.79-16.3) and non-fatal serious adverse events in children (OR 1.62, 95% CI 0.80-3.28) on formoterol with ICS compared to ICS monotherapy was found.[36] Because both fatal and non-fatal serious adverse events are rare, they concluded that the available evidence from the reviews of randomised trials cannot definitively rule out an increased risk.

The FDA performed a meta-analysis of controlled clinical trials comparing the risk of LABA use with no LABA use for different age categories.[19] They found that the composite outcome of asthma-related death, -intubation, or -hospitalization had the highest incidence in the 4-11y age group (30.4 events per 1000 patient years, 95% CI 5.7–55.1). Compared to 4-11y old children not on LABAs the RR was 1.67 (Fig. 2.). These results were similar for patients who reported concomitant use of ICS, though adherence to ICS was not checked. In the small subgroup of patients who were assigned ICS as study medication and whose adherence was checked, there did not seem to be an increased risk.

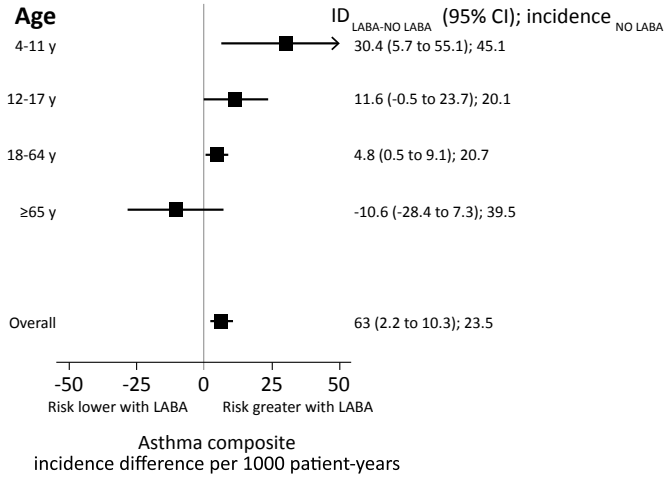

Fig. 2. Incidence difference (ID) per 1000 patient-years for composite outcome of asthma-related death, -hospitalization or -intubation, according to age for LABA versus no-LABA therapy.
LABA = long acting β2-agonist
Incidence$_{No\ LABA}$ = incidence in No LABA group per 1000 patient-years.
Figure adopted from McMahon et al., Pediatrics 2011[19], with permission.

In another pediatric meta-analysis in which 82% of patients used ICS, there was no significant difference (RR 1.05, 95% CI 0.61-1.83) in asthma-related hospitalizations in 4-11y old children on formoterol compared to no LABA.[39] A 2012 Cochrane analysis on the safety of formoterol and salmeterol in asthmatic children (aged 4 -17y) concluded that regular LABA/ICS combination therapy is likely to be less risky than LABA monotherapy.[41]

The important question that remains is whether the benefits of combination therapy in children outweigh the risks. LABA/ICS combination therapy is recommended as a third step in asthma treatment for children > 6 years by clinical guidelines.[3,4] In adults, the addition of a LABA to an ICS improves pulmonary function and symptoms, reduces the use of rescue medication and improves quality of life.[42-44] In children the evidence in favor of LABAs is far less certain, with wide confidence intervals including both superiority and inferiority of LABA/ICS combination therapy compared to the same dose or double dose of ICSs alone.[23,43,44]

It has been postulated that larger trials are necessary to determine the benefits and risks of LABA/ICS combination therapy.[45] In 2011, the FDA issued a requirement for all manufacturers of LABAs to conduct controlled clinical trials to assess the safety of LABA/ICS combination therapy compared to ICS monotherapy.[45] Results from these studies are expected in 2017.[45]

CONCERNS WITH β2-AGONISTS FOR EXERCISE INDUCED BRONCHOCONSTRICTION

β2-Agonists are widely used as prophylactic treatment of EIB. A large body of evidence supports the use of both SABAs and LABAs shortly before exercise.[1] However, regular treatment with β2-agonists leads to tolerance to the bronchoprotective effect of β2-agonists.[1] Both the duration of protection as well as the degree of protection decrease. This loss of protection against EIB with regular LABA treatment has been observed in adults[46,47] and children.[48-50]

Regular treatment with β2-agonists also leads to tolerance to the bronchodilator effect of rescue β2-agonists. It has been a long held believe that tolerance to the bronchodilator effect of β2-agonists does not develop[5], as early studies found no reduction of the bronchodilator effect after regular treatment.[51,52] However, these studies measured the response to a bronchodilator in subjects with an FEV_1 near to normal, leaving little room for improvement with a bronchodilator. In a state of bronchoconstriction, such as in EIB, more β2ARs are necessary to provide sufficient bronchodilation. Studies in asthmatic children[49] and adults[46,53,54] demonstrated bronchodilator tolerance in EIB with regular β2-agonist use, resulting in a reduced response to a rescue SABA, a prolonged recovery

time and the need for extra doses of rescue medication. In adults, bronchodilator tolerance developed within a week of treatment with formoterol.[55] Fortunately, it is also rapidly reversed: three days after formoterol was withdrawn, the bronchodilator response to salbutamol was similar to pre-treatment.[55] No tolerance developed after treatment of asthmatic adults with formoterol three times per week.[56] In clinical practice, the effect of bronchodilator tolerance may therefore be less apparent than in clinical trials due to poor compliance of patients. Children who regularly take a 'drug holiday' might reverse tolerance themselves.

Regular treatment with SABAs has also been described to increase EIB in asthmatic adults.[54,57] An increase in EIB has not been clearly demonstrated after regular treatment with LABA/ICS combination therapy. However, in children with EIB on LABA/ICS combination therapy, withdrawal of the LABA has been shown to improve EIB.[58]

An increase in EIB after regular treatment with β2-agonists could result from downregulation of the β2AR on mast cells, reducing the protective effect of endogenous catecholamines against mediator release by these cells. It could also result from a direct osmotic effect of β2-agonists on the airway mucosa. β2-Agonists stimulate the movement of water across the epithelial cells to the airway surface, which could prime the submucosa to the additional dehydrating effects of exercise.[59] The enhanced need for rescue SABAs due to increased EIB and tolerance to their bronchodilator effect could lead to even more receptor downregulation and a vicious circle of increasing EIB (Fig. 3).

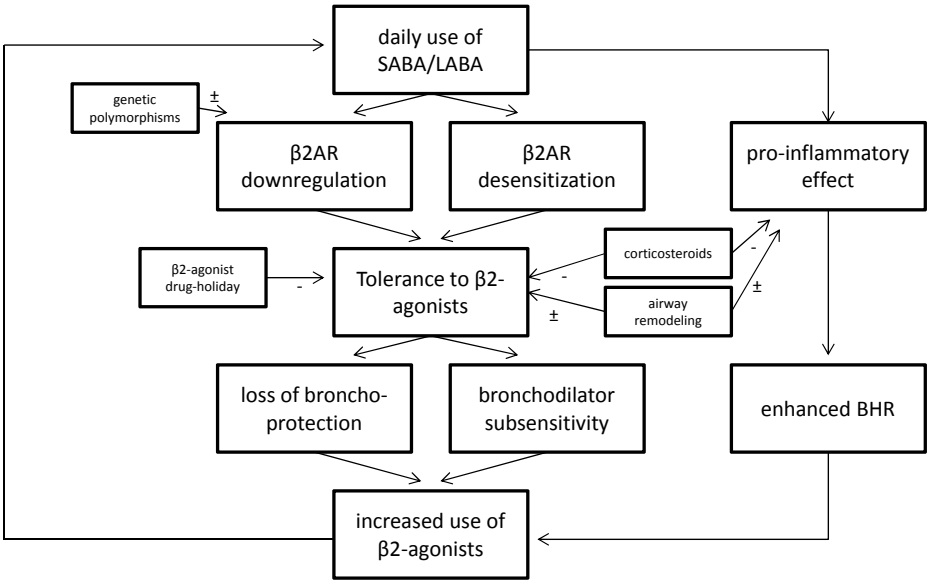

Fig. 3. Schematic representation of vicious circle that could occur with frequent β2-agonist use.
β2AR = β2-adrenoreceptor, LABA = long acting β2-agonist, SABA = short acting β2-agonist.

POSSIBLE MECHANISMS OF INCREASED ADVERSE EVENTS WITH REGULAR β2-AGONISTS

Several mechanisms have been proposed to explain the increase in adverse events with regular β2-agonist treatment.

Masking patients perception of worsening asthma

Since β2-agonists provide good symptom relief, patients may rely on them too much, which may prevent them from taking sufficient anti-inflammatory treatment. Regular treatment with LABAs does not reduce the inflammatory process in the airways[60], but because symptoms are reduced patients are unaware of their underlying disease state and a deterioration of their asthma could be masked. Furthermore, patients may neglect to avoid allergens, as they experience no acute symptoms because of the bronchodilator effect of β2-agonists, causing a more severe late inflammatory response.

Desensitization and downregulation of the β2-adrenoreceptor

The process of desensitization differs from cell to cell. Mast cells and lymphocytes desensitize within 2 min of β2-agonist exposure[61], whereas smooth muscle cells are more resistant. Therefore, β2-agonists can sometimes still exert their bronchodilator effect on airway smooth muscle, without their bronchoprotective effect of stabilizing mast cells. A loss of bronchoprotection could make children more vulnerable to asthma exacerbations in response to allergen, exercise or non specific stimuli.

Furthermore, it has been described that bronchodilator tolerance becomes more apparent with increasing bronchoconstriction[62], such as in an exacerbation. Tolerance to emergency SABA treatment during an exacerbation could lead to life-threatening situations.

Theoretically, corticosteroid induced transcription of the β2AR-gene compensates for receptor downregulation.[63] Both systemic corticosteroids[64] and a single high dose of ICS (1600 µg budesonide)[65] have been shown to reverse bronchodilator tolerance. However, in clinical studies tolerance to the bronchoprotective effects of β2-agonists developed despite concomitant treatment with conventional doses of ICSs.[48-50,53]

Pro-inflammatory and pro-asthmatic effects of β2-agonists

In vitro, LABAs appear to have both anti-inflammatory as well as pro-inflammatory effects. LABAs stabilize mast cells, inhibit plasma exudation, and reduce the adhesion of neutrophils and eosinophils to endothelial cells.[63] Furthermore, LABAs potentiate the anti-inflammatory effects of ICSs.[63]

Regular use of β2-agonists may also paradoxically have a pro-inflammatory effect.[66-69] β2-Agonists induce a shift in peripheral blood mononuclear cells cytokines toward a Th2-

lymphocyte response.[66,67] Regular use of β2-agonists can increase sputum inflammatory cells.[68,69] Clinically, these observations do not appear to be relevant, as a meta-analysis investigating the effect of LABAs on inflammation in adults and children concluded they did not have a clinically important anti- or pro-inflammatory effect.[60]

Sustained exposure to β2-agonists induced 'pro-asthmatic' changes in airway smooth muscle contractility[70] and augmented the effects of bronchoconstrictive mediators[71] and pro-contractile signaling pathways.[72] In a 'proof of principle' study it was demonstrated that 9 weeks treatment with a β-blocker improved BHR to metacholine.[73] These studies indicate that there may be a β2AR-mediated signaling pathway that evokes BHR and thereby worsens asthma control.[74]

Pharmacogenetic effect of β2-adrenoreceptor polymorphisms

β2AR-gene polymorphisms result in changes in the amino acid sequence of the β2AR, leading to alterations of its properties. It was hypothesized that rare variants of the β2AR gene could account for the rare incidence of asthma-related life threatening events in patients receiving regular β2-agonists. The Thr164Ile polymorphism results in a decreased β2AR ligand binding in vitro[75] and was associated with severe exacerbations requiring hospitalizations and systemic corticosteroids in African Americans treated with a LABA.[76]

Two single-nucleotide polymorphisms in specific coding regions, glycine for arginine at codon 16 and glutamic acid for glutamine at codon 27, have been more extensively studied since they are relatively prevalent in Caucasian populations. The Arg16Gly polymorphism has been shown to interfere with treatment responses to β2-agonists. In vitro, receptors with the homozygous Arg16 genotype show enhanced susceptibility for homologous desensitization and receptor downregulation[77], which could account for an increase in β2-agonist tolerance in Arg16 homozygotes.

Both retrospective and prospective analyses of data in adults have demonstrated adverse effects of the Arg16 homozygous genotype on asthma symptoms[78], BHR[79] and exacerbations[80] after receiving a SABA as regular therapy. In the BARGE trial the response to 16-weeks regular albuterol was compared to placebo plus ipratropium rescue treatment in asthmatic adults in a prospective, genotype-stratified, cross-over design.[78] In this study, Arg16 homozygotes did not experience an improvement in PEFR and demonstrated a deterioration of symptom control during albuterol treatment, in contrast to Gly16 homozygotes.

Studies searching for the effect of β2AR genotype on the response to treatment with LABAs have shown conflicting results which appear to be dependent on the age of the study group.

In adults, a large retrospective study in 2250 patients (aged ≥12y) showed no association between LABA treatment and clinical outcomes after stratification by Arg16Gly

genotype.[81] In the LARGE trial the response to 18-weeks twice daily salmeterol (added to ICS) was compared to placebo in a prospective, genotype-stratified, cross-over design.[82] In this study, both Arg16 and Gly16 homozygotes experienced an improvement in lung function, but only Gly16 homozygotes were protected against BHR provoked by methacholine.[82] This loss of bronchoprotection to methacholine after 1-2 weeks of regular LABA use in Arg16 homozygotes was previously described in a retrospective analysis of data from adult asthmatics.[83] However, a prospective trial found no association between Arg16Gly genotype and loss of bronchoprotection to EIB after 2 weeks treatment with salmeterol.[84]

In children, an increased risk for exacerbations in Arg16 homozygotes in a cohort of 1182 patients (aged 3-22y) on daily salmeterol was reported.[85] An increase in oral corticosteroid use and emergency department visits was found in 597 Arg16 homozygotes (aged 4-12y) on LABA/ICS combination therapy, compared to Gly16 homozygotes.[86] A prospective randomized controlled study in asthmatic children aged 5-18y showed that in Arg16 homozygotes adding montelukast compared to salmeterol to inhaled fluticasone significantly improved asthma symptoms, asthma related school absence and quality of life (Fig. 4).[87]

Age related differences in asthma phenotypes

Children appear to have an increased risk of exacerbations associated with regular LABA treatment compared to older age groups (Fig. 2).[19] This could result from differences in the pathophysiology of asthma between adults and children.[88,89]

Airway smooth muscle in children might have a shortened response and relaxation time.[90] BHR to methacholine has a higher reactivity in younger children, in both healthy individuals[91] and asthmatics.[92] Asthmatic children with EIB reach maximal post-exercise bronchoconstriction faster than adults.[90,93] In epidemiologic studies, asthmatic children have a higher incidence of exacerbations than adults.[94] This increased responsiveness of the airway smooth muscle might wane with ageing, as the airways remodel and become more rigid.

Children have relatively unimpaired FEV_1 values.[95] However, in children FEV_1 is not correlated to measures of obstruction in the peripheral airways.[96] The peripheral airways are a major site of the disease process. The density of β2ARs on airway smooth muscle is highest in the peripheral airways. The density of mast cells and activated eosinophils is also increased in the peripheral airways.[95,97] Therefore, undertreatment of the peripheral airways in children with relatively normal FEV_1 values may make them more susceptible to exacerbations and effects of tolerance to β2-agonists.

Possibly adult asthmatics are less vulnerable to the negative effects of β2-agonists due to more airway wall rigidity, caused by remodeling of the bronchoconstrictive ap-

paratus, or due to less atopy, a lower number of inflammatory cells or receptors, or a different affinity of β2ARs to their agonists.

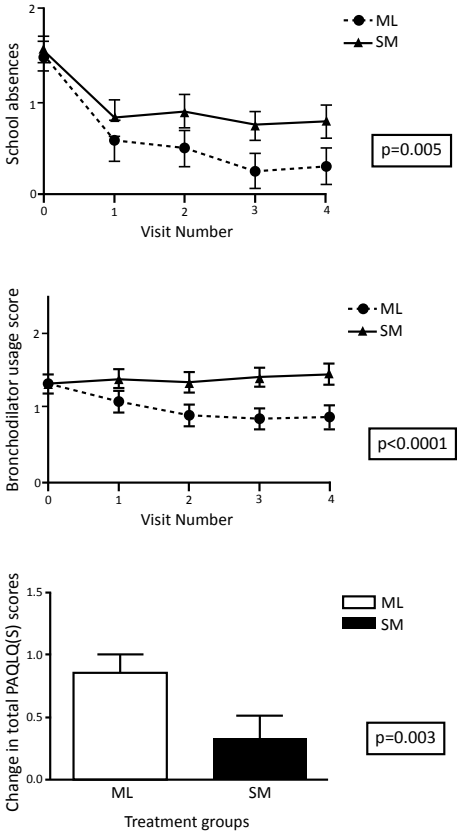

Fig. 4. Changes in asthma-related outcomes in Arg16 homozygous children treated with fluticasone plus oral montelukast (ML) or salmetorol / fluticasone plus placebo montelukast (SM). Visits were every 3 months.
- Top panel: change in asthma-related school absences.
- Middle panel: change in use of salbutamol reliever.
- Bottom panel: change in total pediatric asthma quality of life questionnaire score after 12 months treatment.
Error bars are 95% CI. P-values are shown for the comparison between groups after 12 months. Figure adopted from Lipworth et al.[87], with permission.

CONCLUSIONS & SUGGESTIONS FOR CLINICIANS

Despite the fact that β2-agonists are the most effective bronchodilators currently used, their place in the treatment of childhood asthma and EIB needs to be carefully reconsidered, taking into account possible genetic and environmental influences. For as-needed therapy, SABAs remain the first choice. However, based on the available evidence from clinical trials, it can reasonably be concluded that daily use of SABAs and/or LABAs in the absence of ICS can have adverse effects on asthma control. At the moment, there is no consensus on how to balance benefits and risks of β2-agonist treatment, especially in children under the age of 12, due to a paucity of randomized clinical data for children.[98] More research in children < 12y is necessary to provide evidence based recommenda-

tions on the safety and efficacy of LABA/ICS combination therapy. Based on current evidence and guidelines we would like to suggest the following:

1. Abstain from LABA mono-therapy in children and use LABA/ICS combination therapy only in a single inhaler device

As recommended by the FDA[45] and clinical guidelines[3,4] we should refrain from LABA monotherapy, as it does not treat the underlying inflammation[60], could mask a deterioration of asthma control and is associated with an increased risk of serious adverse events. Combination therapy should be used as a single inhaler to prevent periods of LABA monotherapy due to poor compliance to ICSs.

2. LABA/ICS combination therapy should be used with caution in children aged 4-11 years

In children aged 4-11y, few studies have been performed to compare step-up options when asthma is not well controlled on low-dose ICSs. In contrast to data in adult studies, studies performed in children do not show a significant superior effect of adding a LABA compared to the same dose[43,99] or a double dose[44,100] of ICSs on asthma control, quality of life, BHR and risk of asthma exacerbations, but it does improve lung function. Concomitant use of ICSs possibly mitigates the risk of asthma-related serious adverse events[19], yet the number of pediatric studies is limited and these studies should be interpreted with caution. We suggest to reserve LABA/ICS combination therapy for children aged 4-11y whose asthma is inadequately controlled on a higher dose of ICSs alone, or ICS combined with a leukotriene receptor antagonist.

3. Consider to step-up controller therapy in children with daily use of SABAs for EIB

Although clinical guidelines recommend to step-up anti-inflammatory therapy when SABAs are needed more than twice per week, in clinical practice this usually excludes pre-exercise use. As daily exercise is recommended for all children, including those with asthma, many children use β2-agonists pre-exercise on a daily basis. In children with EIB, daily use of SABAs may lead to an increased maximum fall in FEV_1 after exercise[54,57], a protracted recovery from EIB and tolerance to rescue SABAs. This can compromise athletic performance and participation in active play and sports. Clinicians should consider to step-up controller therapy, such as optimizing the dose of the ICS or adding a leukotriene receptor antagonist, when SABAs are used more than twice weekly, including pre-exercise use.

REFERENCES

1. Bonini M, di Mambro C., Calderon MA, Compalati E, Schunemann H, Durham S, et al. Beta-agonists for exercise-induced asthma. Cochrane Database Syst Rev 2013;10:CD003564.
2. Johnson M. The beta-adrenoceptor. Am J Respir Crit Care Med 1998;158(5 Pt 3):S146-S153.
3. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120(5 Suppl):S94-138.
4. Global initiative for Asthma (GINA). From the Global Strategy for Asthma Managment and Prevention. 2014. Available from: http://www.ginasthma.org/.
5. Sears MR, Lotvall J. Past, present and future-beta2-adrenoceptor agonists in asthma management. Respir Med 2005;99(2):152-70.
6. Rubin BK. Air and soul: the science and application of aerosol therapy. Respir Care 2010;55(7): 911-21.
7. Jones RS, Wharton MJ, Buston MH. The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. Arch Dis Child 1963;38:539-45.
8. Larsson S, Svedmyr N. Bronchodilating effect and side effects of beta2- adrenoceptor stimulants by different modes of administration (tablets, metered aerosol, and combinations thereof). A study with salbutamol in asthmatics. Am Rev Respir Dis 1977;116(5):861-9.
9. Anderson SD, Rozea PJ, Dolton R, Lindsay DA. Inhaled and oral bronchodilator therapy in exercise induced asthma. Aust N Z J Med 1975;5(6):544-50.
10. Cazzola M, Page CP, Rogliani P, Matera MG. beta2-agonist therapy in lung disease. Am J Respir Crit Care Med 2013;187(7):690-6.
11. Taylor DR. The beta-agonist saga and its clinical relevance: on and on it goes. Am J Respir Crit Care Med 2009;179(11):976-8.
12. Szefler SJ, Busse WW. The long-acting beta-adrenergic agonist controversy in asthma: troublesome times! J Allergy Clin Immunol 2012;130(6):1256-9.
13. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006;144(12): 904-12.
14. Salpeter SR, Wall AJ, Buckley NS. Long-acting Beta-Agonists with and without Inhaled Corticosteroids and Catastrophic Asthma Events. Am J Med 2010;123(4):322-8.
15. Wijesinghe M, Weatherall M, Perrin K, Harwood M, Beasley R. Risk of mortality associated with formoterol: a systematic review and meta-analysis. Eur Respir J 2009;34(4):803-11.
16. Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2008;(3):CD006363.
17. Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev 2007;(1):CD001385.
18. Cates CJ, Cates MJ. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2012;4:CD006923.
19. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting beta(2)-adrenergic receptor agonists. Pediatrics 2011;128(5):e1147-e1154.
20. Weatherall M, Wijesinghe M, Perrin K, Harwood M, Beasley R. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. Thorax 2010;65(1): 39-43.

21. Bisgaard H, Szefler S. Long-acting beta2 agonists and paediatric asthma. Lancet 2006;367(9507): 286-8.
22. Castro-Rodriguez JA, Rodrigo GJ. A systematic review of long-acting beta2-agonists versus higher doses of inhaled corticosteroids in asthma. Pediatrics 2012;130(3):e650-e657.
23. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009;(3): CD007949.
24. Johnson M. Molecular mechanisms of beta(2)-adrenergic receptor function, response, and regulation. J Allergy Clin Immunol 2006;117(1):18-24.
25. Peachell P. Regulation of mast cells by beta-agonists. Clin Rev Allergy Immunol 2006;31(2-3): 131-42.
26. Broadley KJ. Beta-adrenoceptor responses of the airways: for better or worse? Eur J Pharmacol 2006;533(1-3):15-27.
27. Stolley PD. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105(6):883-90.
28. Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. Lancet 1989;1(8644):917-22.
29. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med 1994;149(3 Pt 1):604-10.
30. Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336(8728):1391-6.
31. Walters EH, Walters J. Inhaled short acting beta2-agonist use in chronic asthma: regular versus as needed treatment. Cochrane Database Syst Rev 2003;(2):CD001285.
32. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306(6884):1034-7.
33. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129(1):15-26.
34. Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. Ann Intern Med 2008; 149(1):33-42.
35. Jaeschke R, O'Byrne PM, Mejza F, Nair P, Lesniak W, Brozek J, et al. The safety of long-acting beta-agonists among patients with asthma using inhaled corticosteroids: systematic review and metaanalysis. Am J Respir Crit Care Med 2008;178(10):1009-16.
36. Cates CJ, Jaeschke R, Schmidt S, Ferrer M. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2013;6:CD006924.
37. Cates CJ, Jaeschke R, Schmidt S, Ferrer M. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2013;3:CD006922.
38. Nelson H, Bonuccelli C, Radner F, Ottosson A, Carroll KJ, Andersson TL, et al. Safety of formoterol in patients with asthma: combined analysis of data from double-blind, randomized controlled trials. J Allergy Clin Immunol 2010;125(2):390-6.
39. Price JF, Radner F, Lenney W, Lindberg B. Safety of formoterol in children and adolescents: experience from asthma clinical trials. Arch Dis Child 2010;95(12):1047-53.

40. Sears MR, Radner F. Safety of formoterol in asthma clinical trials: an update. Eur Respir J 2014; 43(1):103-14.
41. Cates CJ, Oleszczuk M, Stovold E, Wieland LS. Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. Cochrane Database Syst Rev 2012;10:CD010005.
42. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 2014;1:CD003137.
43. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database Syst Rev 2010;5:CD005535.
44. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010;4:CD005533.
45. Chowdhury BA, Dal PG. The FDA and Safe Use of Long-Acting Beta-Agonists in the Treatment of Asthma. N Engl J Med 2010;362(13):1169-71.
46. Edelman JM, Turpin JA, Bronsky EA, Grossman J, Kemp JP, Ghannam AF, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. Ann Intern Med 2000;132(2):97-104.
47. Villaran C, O'Neill SJ, Helbling A, van Noord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast/Salmeterol Exercise Study Group. J Allergy Clin Immunol 1999;104(3 Pt 1):547-53.
48. Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics 1997;99(5):655-9.
49. Fogel RB, Rosario N, Aristizabal G, Loeys T, Noonan G, Gaile S, et al. Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children. Ann Allergy Asthma Immunol 2010;104(6):511-7.
50. Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. J Allergy Clin Immunol 2008;121(2):383-9.
51. Ekstrom T, Ringdal N, Sobradillo V, Runnerstrom E, Soliman S. Low-dose formoterol Turbuhaler (Oxis) b.i.d., a 3-month placebo-controlled comparison with terbutaline (q.i.d.). Respir Med 1998; 92(8):1040-5.
52. D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. JAMA 1994;271(18): 1412-6.
53. Storms W, Chervinsky P, Ghannam AF, Bird S, Hustad CM, Edelman JM. A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. Respir Med 2004;98(11):1051-62.
54. Hancox RJ, Subbarao P, Kamada D, Watson RM, Hargreave FE, Inman MD. Beta2-agonist tolerance and exercise-induced bronchospasm. Am J Respir Crit Care Med 2002;165(8):1068-70.
55. Haney S, Hancox RJ. Rapid onset of tolerance to beta-agonist bronchodilation. Respir Med 2005; 99(5):566-71.
56. Davis BE, Reid JK, Cockcroft DW. Formoterol thrice weekly does not result in the development of tolerance to bronchoprotection. Can Respir J 2003;10(1):23-6.
57. Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med 1996;153(1):65-9.

58. Kersten ET, Driessen JM, van Leeuwen JC, Thio BJ. Pilot study: The effect of reducing treatment on exercise induced bronchoconstriction. Pediatr Pulmonol 2010;45(9):927-33.
59. Anderson SD, Brannan JD. Long-acting beta 2-adrenoceptor agonists and exercise-induced asthma: lessons to guide us in the future. Paediatr Drugs 2004;6(3):161-75.
60. Sindi A, Todd DC, Nair P. Antiinflammatory effects of long-acting beta2-agonists in patients with asthma: a systematic review and metaanalysis. Chest 2009;136(1):145-54.
61. McGraw DW, Liggett SB. Heterogeneity in beta-adrenergic receptor kinase expression in the lung accounts for cell-specific desensitization of the beta2-adrenergic receptor. J Biol Chem 1997; 272(11):7338-44.
62. Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. Eur Respir J 2003;21(5):810-5.
63. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. Eur Respir J 2002;19(1):182-91.
64. Tan KS, Grove A, McLean A, Gnosspelius Y, Hall IP, Lipworth BJ. Systemic corticosteriod rapidly reverses bronchodilator subsensitivity induced by formoterol in asthmatic patients. Am J Respir Crit Care Med 1997;156(1):28-35.
65. Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and beta2-adrenoceptor down-regulation after regular inhaled formoterol. Chest 1999;115(3):623-8.
66. Agarwal SK, Marshall GD, Jr. Beta-adrenergic modulation of human type-1/type-2 cytokine balance. J Allergy Clin Immunol 2000;105(1 Pt 1):91-8.
67. Panina-Bordignon P, Mazzeo D, Lucia PD, D'Ambrosio D, Lang R, Fabbri L, et al. Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12. J Clin Invest 1997;100(6): 1513-9.
68. Aldridge RE, Hancox RJ, Taylor RD, Cowan JO, Winn MC, Frampton CM, et al. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. Am J Respir Crit Care Med 2000;161(5):1459-64.
69. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Jr., Sorkness CA, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA 2001;285(20):2583-93.
70. Nino G, Hu A, Grunstein JS, Grunstein MM. Mechanism regulating proasthmatic effects of prolonged homologous beta2-adrenergic receptor desensitization in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2009;297(4):L746-L757.
71. McGraw DW, Almoosa KF, Paul RJ, Kobilka BK, Liggett SB. Antithetic regulation by beta-adrenergic receptors of Gq receptor signaling via phospholipase C underlies the airway beta-agonist paradox. J Clin Invest 2003;112(4):619-26.
72. Yang Z, Cooper PR, Damera G, Mukhopadhyay I, Cho H, Kehrl JH, et al. Beta-agonist-associated reduction in RGS5 expression promotes airway smooth muscle hyper-responsiveness. J Biol Chem 2011;286(13):11444-55.
73. Hanania NA, Singh S, El-Wali R, Flashner M, Franklin AE, Garner WJ, et al. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. Pulm Pharmacol Ther 2008; 21(1):134-41.
74. Nino G, Grunstein MM. Current concepts on the use of glucocorticosteroids and beta-2-adrenoreceptor agonists to treat childhood asthma. Curr Opin Pediatr 2010;22(3):290-5.
75. Green SA, Rathz DA, Schuster AJ, Liggett SB. The Ile164 beta(2)-adrenoceptor polymorphism alters salmeterol exosite binding and conventional agonist coupling to G(s). Eur J Pharmacol 2001;421(3):141-7.

76. Ortega VE, Hawkins GA, Moore WC, Hastie AT, Ampleford EJ, Busse WW, et al. Effect of rare variants in ADRB2 on risk of severe exacerbations and symptom control during longacting beta agonist treatment in a multiethnic asthma population: a genetic study. Lancet Respir Med 2014;2(3): 204-13.
77. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol 1995;13(1): 25-33.
78. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004;364(9444):1505-12.
79. Hancox RJ, Sears MR, Taylor DR. Polymorphism of the beta2-adrenoceptor and the response to long-term beta2-agonist therapy in asthma. Eur Respir J 1998;11(3):589-93.
80. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. Thorax 2000; 55(9):762-7.
81. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. Lancet 2007;370(9605):2118-25.
82. Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet 2009; 374(9703):1754-64.
83. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. Br J Clin Pharmacol 2004;57(1):68-75.
84. Bonini M, Permaul P, Kulkarni T, Kazani S, Segal A, Sorkness CA, et al. Loss of salmeterol bronchoprotection against exercise in relation to ADRB2 Arg16Gly polymorphism and FeNO. Am J Respir Crit Care Med 2013;188(12)1407-12.
85. Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. J Allergy Clin Immunol 2009;124(6):1188-94.
86. Zuurhout MJ, Vijverberg SJ, Raaijmakers JA, Koenderman L, Postma DS, Koppelman GH, et al. Arg16 ADRB2 genotype increases the risk of asthma exacerbation in children with a reported use of long-acting beta2-agonists: results of the pacman cohort. Pharmacogenomics 2013;14(16): 1965-71.
87. Lipworth BJ, Basu K, Donald HP, Tavendale R, Macgregor DF, Ogston SA, et al. Tailored second-line therapy in asthmatic children with the Arg(16) genotype. Clin Sci (Lond) 2013;124(8):521-8.
88. Jenkins HA, Cherniack R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. Chest 2003;124(4):1318-24.
89. Gelfand EW. Pediatric asthma: a different disease. Proc Am Thorac Soc 2009;6(3):278-82.
90. Vilozni D, Szeinberg A, Barak A, Yahav Y, Augarten A, Efrati O. The relation between age and time to maximal bronchoconstriction following exercise in children. Respir Med 2009;103(10):1456-60.
91. Hopp RJ, Bewtra A, Nair NM, Townley RG. The effect of age on methacholine response. J Allergy Clin Immunol 1985;76(4):609-13.

92. Mochizuki H, Shigeta M, Kato M, Maeda S, Shimizu T, Mirokawa A. Age-related changes in bronchial hyperreactivity to methacholine in asthmatic children. Am J Respir Crit Care Med 1995; 152(3):906-10.
93. van Leeuwen JC, Driessen JM, de Jongh FH, Anderson SD, Thio BJ. Measuring breakthrough exercise-induced bronchoconstriction in young asthmatic children using a jumping castle. J Allergy Clin Immunol 2013;131(5):1427-9.
94. Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma--United States, 1980-2004. MMWR Surveill Summ 2007;56(8):1-54.
95. Gelfand EW, Kraft M. The importance and features of the distal airways in children and adults. J Allergy Clin Immunol 2009;124(6 Suppl):S84-S87.
96. Keen C, Olin AC, Wennergren G, Gustafsson P. Small airway function, exhaled NO and airway hyper-responsiveness in paediatric asthma. Respir Med 2011;105(10):1476-84.
97. Carroll NG, Mutavdzic S, James AL. Distribution and degranulation of airway mast cells in normal and asthmatic subjects. Eur Respir J 2002;19(5):879-85.
98. Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists--the influence of values. N Engl J Med 2009;360(16):1592-5.
99. Sorkness CA, Lemanske RF, Jr., Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. J Allergy Clin Immunol 2007;119(1):64-72.
100. Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, Brackel HJ, Gerrits GP, Hop WC, et al. Combination Therapy Salmeterol/Fluticasone Versus Doubling Dose of Fluticasone in Children With Asthma. Am J Respir Crit Care Med 2010;182(10):1221-7.